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EXAMINER

FORD, VANESSA L

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/675,172	Applicant(s) DONOVAN, STEPHEN	
	Examiner VANESSA L. FORD	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 March 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 22-28,36 and 37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 22-28,36 and 37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

FINAL ACTION

1. This Office Action is responsive to Applicant's response filed March 10, 2009. Claims 1-21 and 29-35 have been canceled. Claims 22-28 and 36-37 are under examination.

Rejection Maintained

2. The rejection of claims 22-24, 28 and 36 under 35 U.S.C. 103(a) is maintained for the reasons set forth on pages 3-7, paragraph 3 of the previous Office Action.

The rejection is reiterated below:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 22-24, 28 and 36 are rejected under 35 U.S.C. 103(a) as unpatentable over Pearce et al (*U.S. Patent No. 6,087,327 issued July 11, 2000*) in view of Mohr et al (*U.S. Patent No. 5,591,767 issued January 7, 1997*) and further in view of Singer et al (*Acad Emerg Med, Nov. 1998; 5(11), p. 1051-6*) (*Abstract only*).

Independent claim 22 is drawn to a method of reducing neurotransmitter release in a subdermal structure of a patient, the method comprising the steps of: (a) non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum and (b) applying a fluid to the patient's skin, (c) applying a transdermal patch to the skin of a patient in an area that had the stratum corneum disrupted in step (a), the transdermal patch comprising; i) a pharmaceutical composition comprising a stabilized botulinum toxin provided in a dried state and an enhancing agent that is mixable with the stabilized botulinum toxin provided in a dried state and facilitates transdermal administration of a botulinum toxin in a bioactive form to a subdermal target site of a human patient without being administered to the patient's circulatory system; and ii) an adhesive layer disposed to one side of the transdermal patch to removably secure the patch on the patient's skin; when the pharmaceutical composition is incorporated into the adhesive layer; and (d) solubilizing the botulinum toxin provided in the dry state with the fluid, wherein solubilization of the botulinum toxin

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permits diffusion of the botulinum toxin from the adhesive layer into the patient's skin thereby reducing neurotransmitter release in a subdermal structure.

Pearce et al teach that botulinum toxin inhibits or impairs neurotransmitters (column 1). Pearce et al teach that it is contemplated that the neurotoxin would diffuse to the neuromuscular junctions resulting in inhibition of acetylcholine (Ach) release, for example and at sufficiently high dosages complete paralysis of the muscle will occur (column 9). Thus, Pearce et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient. Pearce et al teach that the admixtures used in the invention include botulinum toxins A-G (see the Abstract)(claim 28). Pearce et al teach that the transdermal delivery of botulinum toxin comprising a depot (botulinum toxin in the dried state) administration of botulinum toxin into a selected area (column 9). Pearce et al teach that gelatin to be used in pharmaceutical compositions (column 9). Pearce et al teach that the botulinum toxin compositions are dried (columns 8-9). Pearce et al teach that the depots of the invention can be used in transdermal diffusion (column 9).

Pearce et al do not teach a transdermal patch.

Mohr et al teach transdermal patches that are adhesive patches wherein the drug and the enhancer (enhancing agent) are formulated into the skin adhesive layer (column 7) (claim 36). Mohr et al teach that the adhesive layer serves both as the enhancer reservoir as well as the adhesive layer which attaches the patch to the patient's skin (column 7). Mohr et al teach that the transdermal patches comprise an impermeable backing layer which is sealed at its periphery to a rate-controlling membrane layer thus defining a drug depot (column 8). Mohr et al teach that the drug depot generally contains the drug and optionally an enhancer and/or gelling components (column 8). Mohr et al teach that an adhesive layer on the rate controlling membrane attaches the patch to the patient's skin (column 8).

Pearce et al nor Mohr et al teach the claim limitation of "non-chemically disrupting the stratum corenum of the patient's skin to reduce impermeability of the stratum" or "wherein the stratum corenum is disrupted by abrasively removing the stratum corenum" or "wherein the stratum corenum is disrupted by applying an adhesive material to the patient's skin and removing the adhesive material applied thereto".

Singer et al teach that tape stripping is an effective in disrupting the stratum corenum barrier (See the Abstract)(claim 23 and 24). Singer et al teach that removal of the cornified layer of skin resulted in a more rapid anesthetic effect of the drug (EMLA cream) (see the Abstract).

It would have been *prima facie* obvious at the time the invention was made to modify the method of reducing neurotransmitter release in a subdermal structure of a patient as taught by Pearce et al to include the transdermal patch of Mohr et al which incorporates drugs and skin enhancers (e.g. botulinum toxin and the enhancing agent) into the adhesive layer and non-chemically disrupting the stratum corenum of the patient's skin to reduce impermeability of the stratum corenum as taught by Singer et al

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because Mohr et al has demonstrated that this design of transdermal patch is simple but effective in delivering drugs to the skin and Singer et al teach that tape stripping enhances absorption of drugs into the skin. It would be expected, absent evidence to the contrary, that a transdermal patch comprising botulinum toxin and an enhancing agent within the adhesive layer would be an effective way to facilitate the delivery of active agents such as botulinum toxin to a subdermal target of a patient's skin that has been non-chemically disrupted by tape stripping. Thus, the combination of references teach the claimed method of reducing neurotransmitter release in a subdermal structure of a patient.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one product, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art that botulinum toxin inhibits or impairs neurotransmitters. See Pearce et al. Transdermal patches that incorporate drugs and skin enhancers into the adhesive layer are known in the art. See Mohr et al. Tape stripping is a non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum. See Singer et al. Thus, it would be obvious to reduce neurotransmitter release in a subdermal structure of a patient by using a transdermal patch that incorporates the drug or enhancing agent or into the adhesive layer and non-chemically disrupting the skin of the patient by tape stripping prior to applying the transdermal patch because *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that it is obvious to use a known technique to improve a known product that is ready for improvement to yield predictable results. The combination of references teach the claimed invention absent convincing evidence to the contrary.

Applicant's Arguments

Applicant urges that Pearce et al do not disclose transdermal delivery of botulinum toxin via a depot but rather discloses implantation of a depot-type release modality. Applicant urges that implantation of a depot-type modality has no relation to transdermal delivery, but rather implantation (i.e. insertion or embedding an object or device surgically) of a drug delivery system. Applicant urges that Pearce et al do not teach that the depots of the invention can be used in transdermal diffusion.

Applicant urges that Pearce et al disclose that the compositions of the invention provide more localized, less widespread denervation, that is the compositions minimize the spread of botulinum toxin and resultant non-localized denervation. Applicant urges that it is stated that this is advantageous because it will not expose the patient to the undesirable and no-specific side-effects caused by diffusion-dependent spreading of botulinum toxin admixtures. Applicant urges that in taking, Pearce et al as a whole it is clear that one the advantages of its admixed compositions is this limiting of the diffusion of the toxin from its point of administration. Applicant urges that a person of ordinary skill in the art would not read Pearce et al which is directed to the opposite effect of the claimed invention, since the claimed invention is directed to enhancing the diffusion of botulinum toxin. Applicant urges that Pearce et al teach diffusion-based methods are directed to achieving the opposite effect of the claimed invention. The claimed invention is to achieving methods to facilitate or enhance diffusion of botulinum toxin. Applicant urges this is why there is no mention of permeation enhancers of transdermal patches taught or suggested in Pearce et al.

Applicant urges that the Office is turning to other references is suggested not by the teaching of Pearce et al but rather by hindsight-cased reconstruction based upon the present claims. Applicant urges that the Office must show that combination of references would have provided one of ordinary skill in the art with a reasonable expectation of success.

Applicant urges that Mohr et al and its disclosure regarding transdermal patches would be properly considered/combined if, one of ordinary skill in the art would be directed to look to the use of transdermal/diffusion enhancers (which are not disclosed in Pearce et al) and secondly one of ordinary skill in the art had reasonable expectation of successful use of such enhancers with the botulinum toxin admixtures. Applicant urges that this is not the case and Mohr et al do not mention botulinum toxin. Applicant urges that it is further noted that Mohr et al do not disclose the method step of applying a fluid to a patient's skin which then will solubilize the botulinum toxin provided in the dry state with this fluid applied to the patient's skin.

Applicant urges that a case of prima facie obviousness has not been made. Applicant urges that *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S. Ct. 1727, 82 U.S.C. P.Q.2d 1385, discloses that obviousness analysis must not be applied in a rigid or formulaic way, such that the TSM test can capture the important insight that a claimed invention is not proved obvious merely by demonstrating that each element was, independently, known in the prior art.

Applicant urges that the inclusion of Singer fails to remedy the primary deficiencies and hurdles.

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Examiner's Response to Applicant's Arguments

Applicant's arguments filed March 10, 2009 have been fully considered but they are not persuasive.

It should be remembered that it is the combination of prior art references that teach or make obvious the claimed invention. The Examiner disagrees with Applicant's characterization of the teachings of Pearce et al. Pearce et al teach compositions comprising botulinum toxin (see the Abstract). Pearce et al teach improved compositions for localization and regional denervation (column 3). Pearce et al teach compositions that cause more localized, longer lasting denervation than heretofore described (column 3). Pearce et al teach that the composition of the invention can be used for topical administration or transdermal delivery (column 9). The compositions of Pearce et al are intended to control or localize delivery of botulinum toxin to a particular area of interest to ensure a long-lasting effect of the botulinum toxin to the selected area of interest (column 9) not to minimize transdermal delivery of the toxin as asserted by Applicant. Pearce et al do not in anyway teach away from enhancing or facilitating topical administration or transdermal delivery.

While it is true, that Pearce et al do not teach a transdermal patch, Mohr et al teach transdermal patches that are adhesive patches where the drug and the enhancer (enhancing agent) are formulated into the skin adhesive layer. Mohr et al teach that the adhesive layer serves both as the enhancer reservoir as well as the adhesive layer which attaches the patch to the patient's skin. Mohr et al teach that the patch design of the invention is governed by several factors: permability of drug to the skin, dose of

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drug required, enhancers used to deliver the drug and the flux rate of drug and enhancer required to achieve a therapeutic effect (column 1). Mohr et al teach a liquid reservoir patch that will deliver drugs to the patient's skin (column 10). Mohr et al teach the reservoir patch contains the active agents which may be dispersed in an enhancer or combination of enhancers and thus, the active agent may be dispersed in a dissolved state (column 8). Therefore, Mohr et al teach the method step of applying a fluid to a patient's skin which then will solubilize the botulinum toxin provided in the dry state with this fluid applied to the patient's skin.

Pearce et al nor Mohr et al teach the claim limitation of "non-chemically disrupting the stratum corenum of the patient's skin to reduce impermeability of the stratum" or "wherein the stratum corenum is disrupted by abrasively removing the stratum corenum" or "wherein the stratum corenum is disrupted by applying an adhesive material to the patient's skin and removing the adhesive material applied thereto".

Singer et al teach that tape stripping method is an effective in disrupting the stratum corenum barrier (See the Abstract)(claim 23 and 24). Singer et al teach that removal of the cornified layer of skin resulted in a more rapid anesthetic effect of the drug.

One of ordinary skill in the art would be motivated to combine the three prior art references as present above because: (a) Pearce et al teach botulinum toxin in dried depot form as well as transdermal delivery of the botulinum toxin and Pearce et al also teach that the botulinum toxin depots can be implanted into devices, (b) Mohr et al

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teach that active agents can be embedded or placed into transdermal patches along with chemical enhancers that facilitate the delivery of the active agent and Mohr et al teach that chemical enhancers effectively penetrate the stratum corneum barrier, and (c) Singer et al teach that tape stripping is an effective method in disrupting the stratum corneum barrier.

It would be expected, absent evidence to the contrary, that a botulinum toxin dried depot and an enhancing agent within the adhesive layer could be implanted or embedded into a transdermal patch to facilitate the delivery of the botulinum toxin to a subdermal target of a patient's skin that has been non-chemically disrupted by tape stripping since Pearce et al teach that it is contemplated by their invention that the neurotoxin would diffuse to the neuromuscular junctions resulting in inhibition of acetylcholine (ACh) (a neurotransmitter) release (column 9). Based on the combination of teachings disclosed in the prior art references, one of ordinary skill in the art would reasonably conclude that mechanically disrupting the skin barrier by tape stripping and applying a chemical enhancer would facilitate the delivery of drugs such as botulinum toxin through the skin via transdermal administration.

To address Applicant's comments regarding, *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S. Ct. 1727, 82 U.S.C. P.Q.2d 1385 discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. As discussed above, one of ordinary skill in the art with a reasonable expectation of success would conclude that using a

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mechanical and chemical disruption of the stratum corneum barrier would provide for an effective method of reducing neurotransmitter release in a subdermal structure of a patient by transdermally administering botulinum toxin via a transdermal patch.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In view of all of the above, this rejection is maintained.

3. The rejection of claims 25 and 37 under 35 U.S.C. 103(a) is maintained for the reasons set forth on pages 7-10, paragraph 4 of the previous Office Action.

The rejection is reiterated below:

Claims 25 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pearce et al, Mohr et al, Singer et al as applied to claims 22-24, 28 and 36 above, and further in view of Mitragotri et al (*Science*, Vol. 269, August 11, 1995).

Dependent claims 25 and 37 are drawn to "the method of claim 22, wherein the stratum corneum is disrupted by applying ultrasound at a frequency between 20 kHz to 1 MHz at an intensity that does not permanently damage the patient's skin" and "wherein the ultrasound application is delivered prior to application of the botulinum toxin to the skin".

Pearce et al, Mohr et al, Singer et al have been described previously.

Pearce et al, Mohr et al, Singer et al do not teach dependent claim limitations "the method of claim 22, wherein the stratum corneum is disrupted by applying

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ultrasound at a frequency between 20 kHz to 1 MHz” and “wherein the ultrasound application is delivered prior to application of the botulinum toxin to the skin”.

Mitragotri et al teach a method of applying ultrasound to promote delivering therapeutic doses of proteins across the skin of a patient (see the Abstract). Mitragotri et al teach that the ultrasound is used at a low frequency of about 20 kHz (see p. 852, 2nd col)(claim 25 and 37). Mitragotri et al teach that ultrasound can promote transdermal delivery of high molecular weight proteins (page 850).

It would have been *prima facie* obvious at the time the invention was made to modify the method of reducing neurotransmitter release in a subdermal structure of a patient as taught by Pearce et al to include the transdermal patch of Mohr et al which incorporates drugs and skin enhancers (e.g. botulinum toxin and the enhancing agent) into the adhesive layer, non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum as taught by Singer et al and a method of applying ultrasound to promote delivery of therapeutic doses of proteins across the skin of a patient as taught by Mitragotri et al because Mohr et al has demonstrated that this design of transdermal patch is simple but effective in delivering drugs to the skin, Singer et al teach that tape stripping enhances absorption of drugs into the skin and Mitragotri et al teach a method of applying ultrasound to promote delivery of therapeutic doses of proteins across the skin of a patient. It would be expected, absent evidence to the contrary, that a transdermal patch comprising botulinum toxin and an enhancing agent within the adhesive layer and using ultrasound to enhance delivery of the botulinum toxin to the skin would be an effective way to facilitate the delivery of active agents such as botulinum toxin to a subdermal target of a patient's skin that has been non-chemically disrupted by tape stripping, thereby reduce neurotransmitter release in a subdermal structure of the patient.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one product, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that “The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results”. It well known in the art that botulinum toxin inhibits or impairs neurotransmitters. See Pearce et al. Transdermal patches that incorporate drugs and skin enhancers into the adhesive layer are known in the art. See Mohr et al. Tape stripping is a non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum. See Singer et al. It is well known in the art that ultrasound facilitates the delivery of drugs across the skin of a patient. See Mitragotri et al.

Thus, it would be obvious to reduce neurotransmitter release in a subdermal structure of a patient by using a transdermal patch that incorporates the drug or enhancing agent or into the adhesive layer and non-chemically disrupting the skin of the patient by tape stripping prior to applying the transdermal patch as well as applying ultrasound to facilitate the delivery of the botulinum toxin across the patient's skin because *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses

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that it is obvious to use a known technique to improve a known product that is ready for improvement to yield predictable results. The combination of references teach the claimed invention absent convincing evidence to the contrary.

Applicant's Arguments

Applicant urges that the improper combination of Pearce et al, Mohr et al, Singer et al and the failure of Singer et al to remedy this deficiency as well as the addition of Mitragotri et al to this improper combination is discussed above.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed March 10, 2009 have been fully considered but they are not persuasive.

As discussed above, Pearce et al, Mohr et al, Singer et al teach the claimed invention as it relates to claims 22-24, 28 and 36. One of ordinary skill in the art would be motivated to combine the teachings of Mitragotri et al with the teachings of Pearce et al, Mohr et al and Singer et al because Pearce et al, Mohr et al and Singer et al do not teach dependent claim limitations "the method of claim 22, wherein the stratum corneum is disrupted by applying ultrasound at a frequency between 20 kHz to 1 MHz" and "wherein the ultrasound application is delivered prior to application of the botulinum toxin to the skin".

Mitragotri et al teach a method of applying ultrasound to promote delivering therapeutic doses of proteins across the skin of a patient. Mitragotri et al teach that the ultrasound is used at a low frequency of about 20 kHz. Mitragotri et al teach that ultrasound can promote transdermal delivery of high molecular weight proteins.

Thus, the combination of prior art references teach the claimed invention.

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In view of all of the above, this rejection is maintained.

4. The rejection of claims 26 and 27 under 35 U.S.C. 103(a) is maintained for the reasons set forth on pages 10-13, paragraph 5 of the previous Office Action.

The rejection is reiterated below:

Claims 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pearce et al, Mohr et al, Singer et al, Mitragotri et al as applied to claims 22-25, 28 and 36-37 above, and further in view of Yuzhakov et al (*U.S. Patent No. 6,565, 532 B1 published May 20, 2003*).

Dependent claims 26-27 are drawn to “the method of 22 wherein the stratum corneum is disrupted by passing an electrical current from a first point on the patient’s skin to a second point on the patient’s skin” and “wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin in the subdermal structures”.

Pearce et al, Mohr et al, Singer et al and Mitragotri et al have been described previously.

Pearce et al, Mohr et al, Singer et al and Mitragotri et al do not teach dependent claim limitations “wherein the stratum corneum is disrupted by passing an electrical current from a first point on the patient’s skin to a second point on the patient’s skin” and “wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin in the subdermal structures”.

Yuzhakov et al teach that the drug delivery portion of this invention uses the microneedle array to provide electrodes that apply electric potential between electrodes and one of the electrodes is filled with an ionized drug and the charged drug molecules move into the body to the applied electric potential. Therefore, the claims limitation “wherein the stratum corneum is disrupted by passing electrical current from a first point on the patient’s skin to a second point on the patient’s skin (claim 26)” and “wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin in the subdermal structures (claim 27)” are taught in the prior art reference. Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin comprising providing a microneedle array structure (Abstract and claim 20, column 56). Yuzhakov et al teach that the microneedle array may be contained in a transdermal patch (columns 3-4). Yuzhakov et al teach that botulinum toxin can be delivered through the microneedle array. Yuzhakov et al teach a transdermal patch (columns 3-4) comprising a pharmaceutical composition which comprises a botulinum toxin (column 51, lines 56-63). Yuzhakov et al teach that

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ultrasound may be used to increase transdermal flow rate when used with microneedle arrays of the invention (column 5).

It would have been *prima facie* obvious at the time the invention was made to use the electrodes as taught by Yuzhakov et al in the method of reducing neurotransmitter release in a subdermal structure of a patient because Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin providing a microneedle array structure comprising electrodes. It would be expected, absent evidence to the contrary, to modify the method of reducing neurotransmitter release in a subdermal patient as taught by Pearce et al by using the microneedle array comprising electrodes that apply electric potential to a patient's skin as taught by Yuzhakov et al, the ultrasound applied to a patient's skin according to Mitragotri et al would enhance the delivery of the pharmaceutical compositions (e.g. botulinum toxin and an enhancing agent) incorporated within the adhesive layer of the transdermal patch (as taught by the combination of Mohr et al) into the subdermal layers of a patient's skin which has been non-chemically disrupted as taught by Singer et al.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one product, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art that botulinum toxin inhibits or impairs neurotransmitters. See Pearce et al. Transdermal patches that incorporate drugs and skin enhancers into the adhesive layer are known in the art. See Mohr et al. Tape stripping is a non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum. See Singer et al. It is well known in the art that ultrasound facilitates the delivery of drugs across the skin of a patient. See Mitragotri et al. It is known in the art to move charged drug molecules into the body by applying an electric current. See Yuzhakov et al.

Thus, it would be obvious to combine the transdermal patches which incorporates a drug and enhancing agent within the adhesive layer of a transdermal patch as taught by Mohr et al, wherein the skin of the patient has been non-chemically disrupted by the tape stripping method as taught by Singer et al using the technique of ultrasound as taught by Mitragotri et al to facilitate delivery of the drug through the skin and using the microneedle array to provide electrodes that apply electric potential to the patient's skin to further facilitate the delivery of a drug through a patient's skin as taught by Yuzhakov et al because *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), disclosed that it is obvious to use a known technique to improve a known product that is ready for improvement to yield predictable results. The combination of references teach the claimed invention absent convincing evidence to the contrary.

Applicant's Arguments

Applicant urges that the improper combination of Pearce et al, Mohr et al, Singer et al and Mitragotri et al to this improper combination is discussed above. Applicant urges that the addition of Yuzhakov et al fail to remedy the deficiencies of the other references. Applicant urges that the Examiner misconstrued the meaning of the term "polymers" in column 28 of Yuzhakov et al. Applicant urges that botulinum toxin is mentioned as a part of general list of other types of skin structure modifiers that can be applied through the needle patch.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed March 10, 2009 have been fully considered but they are not persuasive.

As discussed above, Pearce et al, Mohr et al, Singer et al, Mitragotri et al teach the claimed invention as it relates to claims 22-25, 28 and 36-37.

To address Applicant's comments regarding Yuzhakov et al, Yuzhakov et al teach that the drug delivery portion of this invention uses the microneedle array to provide electrodes that apply electric potential between electrodes and one of the electrodes is filled with an ionized drug and the charged drug molecules move through the body to the applied electric potential. Therefore, the claim limitation "wherein the stratum corneum is disrupted by passing electrical current from a first point on the patient's skin to a second point on the patient's skin (claim 26)" and "wherein the

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electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin the subdermal structures (claim 27)" are taught in the prior art reference.

To address Applicant's comments regarding the term "polymer" in column 28 of Yuzhakov et al, Applicants point is well founded. However, Yuzhakov et al do teach polymers as defined as compounds that can be used to remove wrinkles. See column 51. One of ordinary skill in the art would be motivated to use the electrodes as taught by Yuzhakov et al in the method of reducing neurotransmitter release in a subdermal structure of a patient because Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin using a microneedle array structure comprising electrodes. Yuzhakov et al teach that botulinum toxin (a neurotransmitter release inhibitor) can be delivered to the skin using the microneedle array.

To address Applicant's comments regarding botulinum toxin, Yuzhakov et al discloses that botulinum toxin can be used in the claimed invention to modify skin structure.

The combination of prior art references teach the claimed method absent convincing evidence to the contrary.

In view of all of the above, this rejection is maintained.

Status of Claims

5. No claims allowed.
6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Patent Examiner, Art Unit 1645
June 11, 2009